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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,712	11/15/2000	Juergen Schmitz	830003-2002.1	4820

7590 07/08/2005

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/714,712	SCHMITZ ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *155-159 and 161-180* is/are pending in the application.

4a) Of the above claim(s) *168* is/are withdrawn from consideration.

5)☐ Claim(s) *159,161-167,171,196 and 1554* is/are allowed.

6)☐ Claim(s) *172-180* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Claim 168 stands withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to non-elected inventions.

Claims 155-159, 161-167, 169-179, and newly added Claim 180 are being acted upon.

2. In view of Applicant's amendment and remarks filed 4/27/05, the rejection of Claim 157 under the first paragraph of 35 U.S.C. 112 for the introduction of new matter into the claims has been withdrawn. In particular, the Mendez et al. (1997) reference of paragraph 149 does indeed teach the production of fully human antibodies in transgenic mice. The interpretation of the reference disclosed in the specification, however, implies that the antibodies comprise only human V regions. Additionally, Applicant's amendment of Claim 173 has obviated the rejection under the second paragraph of 35 U.S.C. 112.

3. Applicant's request for rejoinder of Claim 168 is acknowledged. Applicant argues that the invention of the claim depends from allowed Claim 155 and thus, meets all the limitations of the claim. Applicant argues that there would be little if any burden to the Office as the novelty and nonobviousness of Claim 155 have been established.

Applicant's request for rejoinder is denied. First, by Applicant's logic, any combination of inventions, daisy-chained together in any way to any allowed claim, should always be rejoined. This is simply not possible. Additionally, the examination of an application comprises additional issues beyond the conclusion of novelty and nonobviousness, e.g., compliance with the first paragraph of 35 U.S.C. 112.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 172-179, and newly added Claim 180, stand/are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) Claim 172, A method for preparing a population of cells enriched for BDCA-2+ cells, comprising contacting a mixture of human cells with an antigen-binding fragment of claim 155 and isolating cells to which the antigen-binding fragment binds.

B) Claim 173, A method of detecting BDCA-2 protein in a biological sample comprising (a) contacting the BDCA-2 protein with the antigen-binding fragment thereof of claim 155 under conditions that permit formation of a complex between the BDCA-2 protein and the antigen-binding fragment; and (b) detecting the formation of the complex.

C) Claim 174, The method of claim 173 wherein the BDCA-2 protein is displayed on the surface of a dendritic cell.

D) Claim 175, The method of claim 174 wherein the step of detecting the formation of the complex comprises detecting at least one metabolic change in the dendritic cell.

E) Claim 176, The method of claim 175 wherein the metabolic change is down-regulation of type I interferon production, down-regulation of Th1 immune responses, induction of intracellular Ca2+ mobilization, or polarization of an immune response to Th2.

F) Claim 177, A method of ligating BDCA-2 antigen on a dendritic cell comprising contacting the cell with the antigen-binding fragment of claim 155.

G) Claim 178, A method of screening for agents that interfere with ligation of BDCA-2, said method comprising contacting a BDCA-2 protein and an antigen-binding fragment of
claim 155 in the presence of a test agent and determining whether the test agent reduces binding of the antigen-binding fragment to the protein.

H) Claim 179, A kit comprising an antigen-binding fragment of claim 155 and at least one component selected from the group consisting of: a buffer, a label, a label conjugated to the antigen-binding fragment and a reagent capable of combining with the antigen binding-fragment.

Applicant's arguments filed 4/27/05 have been fully considered, but they have not been found persuasive.

Regarding Claim 172, Applicant argues that the figure legend of paragraph 70 does indeed support the claim. Applicant now cites paragraph 87 for additional support.

A review of paragraph 70 reveals that the experiment described therein comprises the purification of CD1c+, BDCA2+, BDCA3+ blood DCs. Said cells were purified employing PE-conjugated mAbs and anti-PE-conjugated mAb-microbeads. This clearly is not the generic method of the claim. Paragraph 87

discloses only, "The invention relates to methods of enriching for cell populations enriched in DCs and subsets thereof". In this instance, the cite discloses none of the limitations of the claim.

Regarding Claim 173, Applicant reiterates paragraph 168 of the specification and argues that paragraph 169 is only a particular embodiment of the claimed method. Applicant now cites paragraph 108 and Example 5 in support of the claim. Applicant further argues that the ordinarily skilled artisan would immediately recognize the claimed methods.

A review of paragraph 168 again shows that it does not disclose the limitations of the claim. For example, the claim recites detecting BDCA-2 protein in a biological sample, the specification discloses detecting DCs in a biological sample of soluble BDCa-2 in body fluids. The Examiner's copy of paragraph 108 does not disclose the detection of BDCA-2 protein. Example 5 discloses the detection of DCs and not BDCA-2 protein.

Regarding Claim 174, Applicant indicates confusion with the rejection and points to the Examiner's position regarding the rejection of Claim 173.

Applicant is advised that a dependent claim is read as if it includes the claim from which it depends, thus, Claim 174 recites, "A method of detecting BDCA-2 protein on the surface of a DC comprising …". The cite at paragraph 168 is not limited to BDCA-2 on a DC cell surface.

Regarding Claims 175 and 176, Applicant argues, "The Office acknowledges that claims 175 and 176 are described with regard to monoclonal antibody AC144 but asserts that the description does not extend to other antibodies."

Applicant's assertion is incorrect. The specification fails to support both the detecting of at least one metabolic change, i.e., the generic method, and the generic BDCA-2 antigen-binding fragment.

Applicant further argues that the specification does not suggest that the down-regulation of the type I immune response is limited to the AC144 antibody.

Applicant appears to be arguing that it would be obvious to use other anti-BDCA-2 antibodies in the claimed method. Applicant is advised that it is well-established that the requirement of the first paragraph of 35 U.S.C. 112 is not satisfied by subject matter that is not disclosed, but might be obvious. One shows possession of an invention by describing the invention, including all claimed limitations. *Lockwood v. American Airlines*, 41 USPQ2d 1961 (CAFC 1997), makes clear "all the limitations must appear in the specification". It is the Examiner's position then that "exemplifications" do not support generic embodiments that are not disclosed in the specification.

Regarding Claim 177, Applicant again points to paragraph 240 for support. Applicant cites *Enzo* (2002).

Applicant is again advised that obviousness is not the standard for the introduction of new matter into the claims. That Applicant can find the various words that comprise the claims at various cites throughout the specification does not mean that the specification necessarily supports the claimed invention. In this instance, paragraph 240 discloses BDCA-2 ligation only in the context of down-regulating a Th1 immune response, not in the context of generically ligating BDCA-2 on a DC as is recited in the claim.

Regarding *Enzo* (2002), it is unclear why Applicant would cite case law that has nothing to do with the invention at hand and could actually be used to support the Examiner's position rather than Applicant's. Applicant has wildly misconstrued the holdings in the case and, additionally, supplied a quote completely out of its proper context. The case did not involve antibodies nor methods employing antibodies. Briefly, the court simply held that a deposit of a biological material could, in this case, meet the written description requirement. The court further stated, "Written description requirement for generic claims is not necessarily met as matter of law merely because claim language is repeated verbatim in specification, since, even if claim is supported by specification, language of specification must, to extent possible, describe claimed invention so that one skilled in art can recognize what is claimed, and appearance of mere indistinct words in specification or claim does not satisfy that requirement; specification does not necessarily describe invention by indicating that applicant "possessed" invention as of desired filing date, since ensuring that applicant had possession of

invention is one purpose of description requirement, but possession alone is not always sufficient to satisfy that requirement". This finding could be appropriate in the instant case. Regardless, there is no deposit issue in the instant case and it remains the Examiner's position that the instant specification does not adequately describe the claimed method.

Regarding Claim 179, Applicant argues that the Office has improperly introduced the word "only" into the meaning of the paragraph.

Applicant's argument is acknowledged. However, paragraphs 207-210 still disclose only "anti-DC specific-antigen-binding fragments", the intended use of which, "for measuring BDCA-2" is irrelevant. The specification does not, at this cite, disclose the kit comprising antigen-binding fragment of Claim 155

6. Claims 175 and 176 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth previously, Given the novelty of BDCA-2 antigen-binding fragments, the specification must be looked to for guidance regarding the possible uses of said antigen-binding fragments. A review of the specification discloses just a single BDCA-2 antigen-binding fragment, the AC144 monoclonal antibody. The specification discloses that said antibody when croslinked can induce intracellular CA2+ and that AC144, employed again with a secondary crosslinking antibody, can reduce the production of type I IFN by plasmacytoid DC in response to a single strain of influenza virus or poly I:C.

This limited disclosure does not provide enablement commensurate with the scope of the claims. First, note that in all cases only the AC144 monoclonal antibody was used and always with an additional cross-linking agent. Thus, the induction of intracellular CA2+ or the reduction of type I IFN production most likely requires said cross-linking as it would not be scientifically logical to include the additional reagent absent its necessity. Additionally, whereas just the single antibody was employed in the specification, the claims encompass the use of *any* BDCA-2 antigen-binding fragments. It is well-known in the art that in many instances antibodies binding the same protein have different effects. For example, certain anti-CD3 antibodies are capable of activation T cells whereas others actually block T cell activation. Finally note that the down-regulation of a Th1 response of the polarization towards a Th2 response, limitations for which the specification provides essentially no enablement, would encompass *in vivo* methods of treatment; the experiments disclosed in the specification are not enabling of any *in vivo* methods.

Applicant's arguments filed 4/27/05 have been fully considered, but they have not been found persuasive. Applicant argues antibodies with activity the same as that of AC144 could

be routinely identified. Applicant argues that the secondary cross-linking agent merely served to link cell-bound anti-BDCA-2 antibodies.

While other antibodies similar to AC144 might be found, and secondary cross-linking agents may have merely served to link cell-bound anti-BDCA-2 antibodies, it remains the Examiner's position that the disclosures of Examples 12 and 13 provide insufficient enablement for the broadly claimed methods. Note that the methods encompass a method wherein *any* DC is contacted with *any* BDCA-2 antigen binding fragment and *any* metabolic change indicates binding. Thus, if the DC proliferated, differentiated, or even died, binding of the antigen binding fragment would be detected. Such a method clearly is not enabled by the limited disclosure of the instant specification.

7. The following are new grounds of rejection necessitated by Applicant's amendment.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 178 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically:

A) The claim includes multiple grammatical errors. First, at line 4, "fragment claim 155" should properly be "fragment of claim 155". Second, at line 7, "any one immunologic properties" should properly be "any one immunologic property".

B) The claim is vague and indefinite in the recitation of "whether the test agent modulated any one immunologic properties" as neither "modulated" nor "immunologic properties" are defined. Regarding "modulate", the term is not found in either Stedmans's Medical Dictionary or Biotechterms.org, thus a standard dictionary definition must be sought. The most relevant definition found in Webster's Ninth New Collegiate Dictionary (1990) would be, "to adjust or keep in proper measure or proportion, or to temper". This sort of "adjusting" or "tempering" would seem to comprise a vague and indefinite definition in the instant context and clearly, the metes and bounds of the claim cannot be readily established. Regarding

the "immunologic properties" to be "modulated", while it may seem obvious that "immunologic properties" would include such properties as antigen presentation and T cell activation, it is unclear whether properties such as cell viability or cell differentiation would be encompassed as "immunologic" given that such properties could be said to affect the cells' effects on the immune system.

10. Claim 178 is rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use a method of screening for pharmaceutically effective agents.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

Regarding a claim reciting a pharmaceutical composition, the disclosure must be enabling for the *in vivo* use of the composition identified by the claimed method. A review of the 21 examples in the jumbo specification discloses no pharmaceutical compositions and no examples that would be particularly relevant for the enablement of a pharmaceutical composition. Indeed, the specification fails to even disclose any particular link between BDCA-2, an antibody that binds BDCA-2, and any pharmaceutical compositions. Accordingly the disclosure is insufficient to enable the method of the claims as it would take undue trials and errors to practice the claimed invention.

11. Claim 180, is rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the method of Claim 173 wherein at least 80% of the cells in the population of cells enriched for BDCA-2 cells are BDCA-2 cells.

Applicant's amendment, filed 4/27/05, asserts that support for the new limitations of the claim can be found at paragraph 33 of the specification and in original Claim 62. Said support has not been found; the specification and original claims support a method of obtaining 80% BDCA-2+ cells and not a method of detecting said cells as set forth in Claim 173.

12. Claim 155-159, 161-167, and 169-171 are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

14. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

6/30/05

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